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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/192,064	11/13/1998	HARTOUN HARTOUNIAN	07333/043001	9320

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MASTERMIND IP LAW PC
421-A SANTA MARINA COURT
ESCONDIDO, CA 92029

EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/192,064	HARTOUNIAN ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 6-5-06 is acknowledged.

Claims included in the prosecution are 1-10, 12-35, 49, 51-53, 55-72 and 74-81 and 84-89.

In view of the cancellation of claims 82 and 83, the 102 rejections are withdrawn.

Claim Rejections - 35 U.S.C. ' 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-10, 12-35, 49, 51-53, 55-72, 74-81 and 84-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (cancer Treatment Reports, 1987) or Assil (arch. Ophthalmol. 1987) or Bonetti (Cancer Chemother. Pharmacol. 1994) or Kim (5,723,147), or Sankaram (5,766,627) in view of Lenk (5,48,441), optionally in further combination with Bosworth (5,407,660).

The above references of Kim, 1987, Assil, 1987, Bonetti 1994 or Kim 147 or Sankaram, 627 all teach basically the same process of preparation of multivesicular liposomes.

The process involves dissolving the amphipathic lipid and the neutral lipid in chloroform and mixing it with an aqueous solution containing sucrose and forming an emulsion (instant step A), mixing this emulsion with an aqueous solution (step b) and removing the organic solvent and thereby forming the multivesicular liposomes (note the experimental sections in the publications and examples in Kim 147 and Sankaram 627).

What are lacking in these references are the teachings of filtration by cross-flow filtration method and making a sterile preparation.

Lenk while disclosing a method for size separation of particles teaches that there are problems associated with various methods previously available for the preparation of liposomes or vesicles of a select size and that by the cross-filtration method (also called as tangential flow filtration method) allows one to select large quantities of liposomes of a homogeneous, defined size distribution from a heterogeneously-sized population (note the abstract, col. 4, line 12 through col. 6, line 49). Lenk also discloses preparations for various modes of administration and sterile solutions (note col. 15, lines 1-19 and examples).

The use of cross-flow filtration step in the method of preparation of multivesicular lipid particles of Kim, Assil, Bonetti or Sankaram would have been obvious to one of ordinary skill in the art since Lenk teaches the advantages of using such a step in the preparation of vesicles or liposomes. It is deemed within the skill of the highly developed

sciences to prepare a sterile preparation. It is also within the skill of the art to realize that if any composition is given by a systemic route, in the form of an injection in particular, that the preparation should be sterilized. Furthermore, it is clearly evident from Lenk that sterile preparations have to be used if they are administered to mammals. The criticality of the type of mixers and various method parameters recited in instant claims is not readily apparent to the examiner. In the absence of unexpected and unobvious results, these are deemed to be manipulations of the basic method steps by an artisan to obtain the best possible results. It is common practice in any field to perform a pilot method and extend it to a large-scale production. Similar is the case with the removal of the solvent using a two-step process sparging with different gas flow rates. Since Chloroform is toxic to animals and humans, it is within the skill of the art to recognize that this solvent has to be removed totally before the administration of the liposomes and therefore, one of ordinary skill in the art would flush the mixture with an inert gas such as nitrogen at different flow rates. That the Knowledge in the art of the removal of the organic solvent using a two step process to ensure that the organic solvent is totally removed is evident from the reference of Bosworth (Example 2).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that claim 1 no longer recites a sterilization step, but however, recites a sparging step comprising at least two phases conducted at different gas flow rates and that none of the cited references disclose or suggest such a step for the production of multivesicular liposomes. In response to the examiner's argument that a person of ordinary skill in the art would know to use a multi-step process of solvent

removal employing different gas flow rates and citing Bosworth, applicant argues that the 660 reference discloses a process for making paramagnetic liposome preparation for use in NMR procedures and does not teach or suggest preparation of multivesicular liposomes, which differ greatly from other liposomes in the manner in which they are produced, as well as in the inherent properties that they possess. Applicant further argues that the example 2 in Bosworth pointed out by the examiner removes the solvent using vacuum and not by sparging. These arguments are not found to be persuasive. The examiner cited Bosworth to show the practice in the art to remove the organic solvent using a two-step process to ensure that the **organic solvent** is **totally removed.** The formation of multivesicular liposomes when the solvent is **completely evaporated** and that the evaporation of the solvent can be accomplished by **sparging, rotary evaporation or solvent selective membranes** is taught by Kim (147) on col. 5, lines 25-32. Therefore, it is still the examiner's position that this step is a manipulatable step practiced by an artisan for the **total removal of the organic solvent**. Applicant argues that claims 49, 65, 68, 72, 74-79, 85-86 and 89 recite specific volume fractions required for the first and second emulsions that are necessary for preparing multivesicular liposomes having a predetermined, uniform size distribution. These arguments are not persuasive since the references cited (except Lenk and Bosworth) pertain to the preparation of multivesicular liposomes just as in instant application and the preparation of multivesicular liposomes using specific volumes and having 'defined size distribution is taught for example, by Kim 147 (see abstract). Applicant's arguments that claims 63, 66, 68, 74-79, 87 and 89 recite specific speeds and time parameters and

claims 64, 75 and 88 recite specific velocity and time parameters using static mixture. It is the examiner's position that these are manipulatable parameters practiced by an artisan to obtain the best possible results. The examiner cites the references of West (4,781,871) (see col. 13, line 60 through col. 14, line 9), Weder (5,658,898) (see col. 7, line 25), Frederiksen (5,700,482) (see col. 9, lines 44-45) which show the routine use of static mixtures in liposomal art and the reference of Narula (4,788,001) (see col. 8, lines 9-14) which shows the routine use of impeller mixers for the preparation of emulsions in this context.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK